

REMARKS

Claims 7, 9, 10, and 18-20 are pending in this application.

Applicants acknowledge the withdrawal of all of the rejections set forth in the previous Office Action.

35 U.S.C. § 103

Claims 7, 9, and 18-20

The Office Action alleges that claims 7, 9, and 18-20 are obvious in light of Whittum-Hudson et al. (*Nat. Med.* 2:1116-1121 (1996); hereinafter "Whittum-Hudson"), Stuart et al. (*Immunology* 61:527-533 (1987); hereinafter "Stuart-1987"), Stuart et al. (*Current Microbiol.* 28:85-90 (1994); hereinafter "Stuart-1994"), and Dick, Jr. et al. (*Conjugate Vaccine Contrib. Microbiol Immunol.* 10:48-114 (1989); hereinafter "Dick Jr.").

Applicants respectfully disagree and submit that a *prima facie* case of obviousness has not been established by the Office because this combination of references fails to teach or suggest all of the elements recited in the claims, and fails to provide a motivation to combine these references. Indeed, two of the cited references actually teach away from the claimed subject matter. In addressing the obviousness rejection, applicants will explore the contents of each reference and explain how, when combined, these references fail to render the claimed subject matter obvious.

The Prior Art Fails to Teach or Suggest the Claim Elements

Claim 7 recites a composition that includes a carrier group covalently coupled to one or more isolated oligosaccharides that are cleaved from, or are chemically synthesized to correspond to oligosaccharides cleaved from, a chlamydial glycolipid exoantigen (GLXA). As described in detail below, the cited references, whether considered alone or in combination, fail to teach or suggest covalently coupling one or more isolated GLXA oligosaccharides to a carrier group.

The Office Action concedes at page 4 that “Whittum-Hudson et al do not teach an isolated GLXA oligosaccharide.” To the contrary, Whittum-Hudson at page 1118 indicates that the authors used only whole GLXA to conduct its studies (i.e., GLXA with its complete lipid and polysaccharide components). Thus, this reference does not teach or suggest that one or more oligosaccharides should be isolated (e.g., cleaved from), or chemically synthesized to correspond to oligosaccharides cleaved from, GLXA and then covalently coupled to a carrier group. The remaining references fail to provide the information missing from Whittum-Hudson.

The Office Action at page 4 discusses Stuart-1987, alleging that this reference “teach[es] an isolated polysaccharide component (GLXA oligosaccharide) (pages 527-530). Stuart et al. 1987 teach that the polysaccharide component is antigenic (page 527).” Applicants disagree with this characterization because this reference, even in combination with the other cited references, does not teach or suggest isolating a GLXA oligosaccharide, and certainly does not suggest covalently coupling an isolated GLXA oligisaccharide to a carrier. Rather, Stuart-1987 studied the composition of GLXA, e.g., the sugars present, the molecular weight, which components are antigenic, and the types of fatty acids present in GLXA. In fact, Stuart-1987 discloses that both the lipid and polysaccharide components of GLXA are antigenic. Stuart-1987 fails to lead skilled practitioners to isolated oligosaccharides as opposed to the other GLXA components, or to suggest coupling the oligosaccharide component, rather than another component, to a carrier group.

The Office Action at page 4 cites Stuart-1994 to support the proposition that “the epitope on the polysaccharide component is recognized and binds to the monoclonal antibody 89MS30.” However, this reference discloses only that whole GLXA reacts with 89MS30. This becomes clear, for example, at page 86 (“Antigen preparation”), which discloses that the antibody was used to purify GLXA from the supernatant of *C. trachomatis*-infected cell cultures. Figure 3 of Stuart-1994 demonstrates that GLXA and cell culture supernatants (which contain GLXA) both react with 89MS30. Stuart-1994 did not isolate the polysaccharide component of GLXA, nor does this reference indicate that the epitope recognized by 89MS30 resides in the polysaccharide component of GLXA. As such, this reference provides no teaching or suggestion to isolate one

or more oligosaccharides from GLXA and covalently couple them to a carrier group, or that the 89MS30 antibody binds to one or more GLXA oligosaccharides.

Next with respect to Dick Jr., the Office Action at pages 4-5 alleges that

Dick, Jr. et al teach conjugation of bacterial carbohydrate (polysaccharide) antigens to a carrier protein ... Dick, Jr. et al teach that it is well established that covalent bonding of carbohydrate antigens to proteins can transform the carbohydrate into the status of a TD antigen (pages 49 and 56). Dick, Jr. et al teach that CPS can be linked to carrier proteins directly or by bifunctional linkers (spacer arms) (pages 71-72) which overcome conjugation limitations imposed by steric effects (page 71). Dick, Jr. et al teach that linkers can promote improved antigenicity for the bound components as compared to results obtained when testing the same antigens conjugated by a direct method (page 72). Dick, Jr. et al teach that spacers (i.e. linkers) permit corresponding increases in translational and rotational characteristics of the antigens, increasing access of the binding sites to soluble antigens (page 72). Dick, Jr. et al teach that linkers can be covalently bound to carbohydrate components (page 70).

Applicants respectfully disagree with the Office's assessment of Dick Jr. because this reference merely discloses the preparation of glycoconjugates of carbohydrates from capsular polysaccharide (CPS) and lipopolysaccharide (LPS), both of which are present on cell surfaces (unlike GLXA, which is secreted, see, e.g., Stuart-1994, Abstract, "Chlamydia secrete a genus-specific glycolipid antigen (GLXA) into the supernatant of infected cell cultures."). Dick Jr. indicates that glycoconjugates can be made from pathogens that "share an important common characteristic: elaboration of specific and essentially unique carbohydrate components" (page 48). Pages 58-60 of Dick Jr. describe the selection of a carbohydrate antigen, but the only types of carbohydrates suggested for use are those isolated from two cell surface antigens: CPS and LPS. Dick Jr. concludes at page 96, stating, "Conjugate vaccines offer a bright promise in reducing morbidity and mortality for diseases caused by bacteria elaborating a poly(oligo)meric carbohydrate fraction, either as CPS or LPS" (emphasis added). Dick Jr. fails to offer any teaching or suggestion about GLXA, or any other secreted glycolipids, much less a teaching or suggestion that one or more oligosaccharides should be isolated from GLXA and coupled to a carrier.

None of the cited references teach or suggest coupling one or more isolated GLXA oligosaccharides to a carrier group. Thus, the references, even when considered in combination, fail to teach or suggest all of the claim elements. Applicants therefore submit that the Office has failed to establish a *prima facie* case for obviousness of claims 7, 9, 18-20.

The Cited References Fail to Provide a Suggestion or Motivation to Combine the References

Applicants submit that the references cited in the Office Action fail to provide a motivation to combine their disclosures. In fact, as discussed below, two of the cited references actually teach away from doing so.

The Office Action states at pages 5-6:

It would be expected barring evidence to the contrary, a composition comprising GLXA covalently coupled to a carrier protein would be effective in stimulating a response from the immune system since the polysaccharide component has been demonstrated to be antigenic.

Applicants submit that the “evidence to the contrary” to which the Office refers does in fact exist. Indeed, Whittum-Hudson and Stuart-1994 both teach away from covalently coupling of one or more isolated GLXA oligosaccharides to a carrier. The pathogenesis of Chlamydia infection is complicated, and what was known at the present application’s filing date would not have provided skilled practitioners with a motivation to combine the cited references to arrive at the claimed compositions.

Whittum-Hudson discloses that serum from subjects infected with Chlamydia reacts with GLXA, yet the subjects still suffer from the Chlamydia infection. Thus, the presence of antibodies specific to GLXA do not cure subjects of their Chlamydia infection (page 1116, right column). Further, Whittum-Hudson states that subjects that had a past Chlamydia infection (and possess anti-GLXA antibodies) do not possess protective immunity against future re-infection (page 1116, left column). Next, Whittum-Hudson demonstrates (on page 1118) that when mice were immunized with either a soluble anti-idiotypic antibody (mAb₂) or with whole GLXA, only the mAb₂ was protective against subsequent chlamydial challenge: “Significant reductions in

infectious yields were observed [after immunization with mAb₂] even after a >2 log higher challenge dosage, whereas GLXA in alumina was not protective" (emphasis added). A skilled practitioner, upon reading Whittum-Hudson's statements that whole GLXA was not protective, would have had no motivation whatsoever to isolate one or more oligosaccharides from GLXA and to couple them to a carrier, because she would not have had any reason to believe the resulting composition would generate a protective immune response. Thus, there was simply no reason, and thus no motivation, to make the claimed composition.

Stuart-1994 also teaches away from covalently coupling one or more isolated GLXA oligosaccharides to a carrier. Stuart-1994 describes the potential role for GLXA during the course of a Chlamydia infection:

During chlamydial infection in vivo, extracellular GLXA could accumulate prior to EB [elementary body] release, complex with the anti-GLXA antibody, and thereby protect infectious EB from neutralization; this hypothesis currently is being tested. The results may define a 'smoke screen' role [15] as one biologic function for extracellular GLXA as well as establishing GLXA as a molecule important to immunity. (page 90; emphasis added)

As this passage indicates, GLXA is thought to distract a subject's immune system by causing the immune system to generate antibodies against the secreted GLXA as opposed to generating antibodies against the organism itself. As a result of GLXA "distracting" the immune system, Chlamydia can establish an infection in the subject. Thus, skilled practitioners reading Stuart-1994 would have concluded that any antibodies specific to GLXA would be ineffective in treating or preventing a Chlamydia infection because of the known smoke screen effect. As a result, skilled practitioners would not have been motivated to isolate a GLXA oligosaccharide and couple it to a carrier, or to use such a composition as a Chlamydia vaccine.

The Office Action at page 6 states that

One of skill in the art would have been motivated to produce the immunogen as combined because Stuart et al, 1987 teach that GLXA polysaccharide is antigenic and suggest that it is reasonable to assume that soluble antigens may play a role in the immunopathology associated with diseases caused by Chlamydia (page 533). Additionally, Dick, Jr. et al teach that glycoconjugate vaccines directed against pathogenic bacteria are known in the art. See Table 1.

However Stuart-1987 merely discloses that both the lipid and polysaccharide components of GLXA are antigenic, and says nothing about these components generating protective immunity. No skilled practitioner would have been motivated by Stuart-1987 to focus on the polysaccharide component as opposed to the lipid component or whole GLXA molecule, isolate an oligosaccharide therefrom, and couple it to a carrier. Also, to provide a clear record, applicants point out that the complete passage from Stuart-1987 that the Office paraphrases at page 6 states that “It is reasonable to assume that soluble antigens released from infected cells would react with ligands of the host defence system, leading to hypersensitive reactions that could contribute to the immunopathology associated with chlamydial disease sequelae” (page 533; emphasis added). The soluble antigen referred to in this passage is whole GLXA, not an oligosaccharide isolated therefrom. This passage in no way suggests that an oligosaccharide should be isolated from GLXA, much less that such an isolated oligosaccharide should be coupled to a carrier in an attempt to arrive at an anti-Chlamydia vaccine. Neither this passage nor any other passage in Stuart-1987 offers any motivation to couple one or more isolated oligosaccharides from GLXA to a carrier.

Dick Jr. also fails to offer any motivation to combine the references to arrive at the claimed subject matter. As mentioned above, Dick Jr.'s disclosures are limited to cell surface antigens, CPS and LPS, and do not teach about secreted antigens, much less about GLXA in particular. Dick Jr. offers no motivation to practice its techniques in an attempt to prepare a composition to treat Chlamydia infection. Dick Jr. provides a long list of bacteria from which cell surface antigens can be isolated, e.g., *Haemophilus influenzae*, *Neisseriae meningitidis*, *Streptococcus pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Cryptococcus neoformans*, *Escherichia coli*, *Klebsiella*, and *Vibrio cholerae* (page 48). Tellingly, Chlamydia and GLXA are not listed in the text, nor are they listed in the examples in Table 1 of Dick Jr.

Finally, as discussed above, Whittum-Hudson and Stuart-1994 actually teach away from covalently coupling one or more isolated GLXA oligosaccharides to a carrier. Thus, applicants respectfully submit that a motivation to combine the cited references is lacking, and as a result,

that a *prima facie* case of obviousness has not been established. Applicants request that the obviousness rejection of claims 7, 9, and 18-20 be withdrawn.

Claim 10

The Office Action alleges that claim 10 is obvious in light of Whittum-Hudson, Stuart-1987, Stuart-1994, Dick Jr., and either Semprevivo ((*Carbohydrate Research* 177:222-227 (1988); hereinafter "Semprevivo"), or alternatively, Smith (*J. Biol. Chem.* 255:55-59 (1980); hereinafter "Smith"). Applicants respectfully disagree because the teachings of Semprevivo and Smith fail to correct the deficiencies of the other references described above. As claim 10 depends from claim 7, applicants point out that it is therefore patentable for the reasons articulated above.

The Office Action relies on Semprevivo or Smith for their teaching of a 2-(4-aminophenyl)ethylamine linker. For both of these rejections, the Office Action alleges that it would have been *prima facie* obvious to use the 2-(4-aminophenyl)ethylamine linker as taught by Semprevivo or Smith to covalently couple the carrier group "to the oligosaccharide as taught by the combined art references (Whittum-Hudson et al, Stuart, 1987, Stuart 1994, and Dick, Jr. et al)" (see, e.g., pages 7 and 9). As discussed above, Whittum-Hudson, Stuart-1987, Stuart-1994, and Dick Jr. all fail to teach or suggest one or more isolated GLXA oligosaccharides coupled to a carrier. Neither Semprevivo nor Smith make up for this deficiency because neither describes or suggests coupling an isolated GLXA oligosaccharide to a carrier.

Semprevivo describes a method for derivatizing oligosaccharides from the eukaryotic organism *Leishmania mexicana amazonensis*, and indicates that similar methods have been utilized for other eukaryotic organisms, such as *Leishmania tropica*, *Leishmania donovani*, *Trichomonas vaginalis*, *Schistosoma mansoni*, and *Nematospiroides dubius*. However, Chlamydia is a prokaryotic organism and nothing in Semprevivo teaches or suggests that its methods could be used to couple one or more isolated oligosaccharides from a prokaryote, much less from chlamydial GLXA specifically, to a carrier. Smith describes a method for derivatizing free sialylated oligosaccharides from human milk. There is no teaching or suggestion in Smith

that methods used to couple a sialylated oligosaccharide from human milk could be practiced with one or more isolated chlamydial GLXA oligosaccharides. Because the combined references fail to teach or suggest all of the elements recited in the claims, applicants submit that a *prima facie* case of obviousness has not been established and request that the obviousness rejection of claim 10 be withdrawn.

Neither Semprevivo nor Smith provides a motivation to combine the references or a reasonable expectation of success if the references were combined. Semprevivo describes only the conjugation of oligosaccharides from eukaryotic organisms. Smith also fails to provide a motivation to combine the references or a reasonable expectation of success if the references were combined, and only describes the use of sialylated human milk oligosaccharides to generate antibodies. In reading either Semprevivo or Smith, alone or in combination with Whittum-Hudson, Stuart-1987, Stuart-1994, and Dick Jr., skilled practitioners would have found no motivation to prepare the composition recited in the claims. Furthermore, as discussed above, Whittum-Hudson and Stuart-1994 actually teach away from the claimed subject matter.

Because the combined references fail to teach or suggest all of the elements recited in the claims, and fail to provide a motivation to combine the references or a reasonable expectation of success, applicants respectfully submit that a *prima facie* case of obviousness has not been established and request that the obviousness rejection of claim 10 be withdrawn.

CONCLUSION

Applicants respectfully request that the rejections to claims 7, 9, 10, and 18-20 be withdrawn and that the claims be allowed.

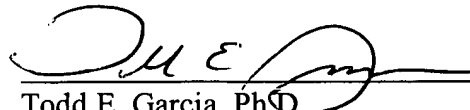
Applicant : Elizabeth S. Stuart et al.
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Enclosed is a \$60 check for the Petition of Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 08952-008001.

Respectfully submitted,

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